UNITED STATES
SECURITIES AND EXCHANGE COMMISSION
Washington, D.C. 20549

FORM 8-K

CURRENT REPORT
Pursuant to Section 13 or 15(d) of the Securities Exchange Act of 1934

December 14, 2023
Date of Report (Date of earliest event reported)

Bicycle Therapeutics plc
(Exact name of registrant as specified in its charter)

England and Wales	**001-38916**	**Not applicable**
(State or other jurisdiction of incorporation)	(Commission File Number)	(IRS Employer Identification No.)

Blocks A & B, Portway Building, Granta Park Great Abington, Cambridge United Kingdom	**CB21 6GS**
(Address of principal executive offices)	(Zip Code)

Registrant's telephone number, including area code: **+44 1223 261503**

Check the appropriate box below if the Form 8-K filing is intended to simultaneously satisfy the filing obligation of the registrant under any of the following provisions:

☐ Written communications pursuant to Rule 425 under the Securities Act (17 CFR 230.425)

☐ Soliciting material pursuant to Rule 14a-12 under the Exchange Act (17 CFR 240.14a-12)

☐ Pre-commencement communications pursuant to Rule 14d-2(b) under the Exchange Act (17 CFR 240.14d-2(b))

☐ Pre-commencement communications pursuant to Rule 13e-4(c) under the Exchange Act (17 CFR 240.13e-4(c))

Securities registered pursuant to Section 12(b) of the Act:

Title of each class	Trading Symbol(s)	Name of each exchange on which registered
Ordinary shares, nominal value £0.01 per share	n/a	The Nasdaq Stock Market LLC*
American Depositary Shares, each representing one ordinary share, nominal value £0.01 per share	BCYC	The Nasdaq Stock Market LLC

***** Not for trading, but only in connection with the listing of the American Depositary Shares on The Nasdaq Stock Market LLC.

Indicate by check mark whether the registrant is an emerging growth company as defined in Rule 405 of the Securities Act of 1933 (§ 230.405 of this chapter) or Rule 12b-2 of the Securities Exchange Act of 1934 (§ 240.12b-2 of this chapter).

Emerging growth company ☐

If an emerging growth company, indicate by check mark if the registrant has elected not to use the extended transition period for complying with any new or revised financial accounting standards provided pursuant to Section 13(a) of the Exchange Act. ☐

Item 8.01 Other Events.

On December 14, 2023, Bicycle Therapeutics plc (the "Company") issued a press release announcing data updates for three clinical programs and an overview of its Research & Development (R&D) strategy at its previously announced first R&D Day in New York City. A copy of the press release is attached as Exhibit 99.1 to this Current Report on Form 8-K and is incorporated into this Item 8.01 by reference.

Also on December 14, 2023, the Company hosted the above-mentioned R&D Day. A copy of the presentation used in the conference call can be accessed by visiting the "Presentation + Events" section at investors.bicycletherapeutics.com.

Item 9.01 Financial Statements and Exhibits

(a) Exhibits

99.1	Press Release dated December 14, 2023
104	Cover Page Interactive Data File (embedded within the Inline XBRL document)

SIGNATURES

Pursuant to the requirements of the Securities Exchange Act of 1934, the registrant has duly caused this report to be signed on its behalf by the undersigned hereunto duly authorized.

Date: December 14, 2023

BICYCLE THERAPEUTICS PLC

By: /s/ Alethia Young
Name: Alethia Young
Title: Chief Financial Officer

Exhibit 99.1

Bicycle Therapeutics Provides Data Updates for Three Clinical Programs and Strategy Overview at First R&D Day

Nectin-4 portfolio comprised of BT8009 and BT7480 represents potential opportunity to become leader in treating Nectin-4-driven cancers, starting with metastatic urothelial cancer (mUC)

Updated BT8009 clinical data continue to support promising response and differentiated safety profile in mUC as well as emerging clinical activity in additional tumor types beyond bladder

EphA2 portfolio led by BT5528 could be the first to address a historically undruggable target widely expressed in many cancers

Additional work in oncology and beyond highlight the breadth of the Bicycle® platform and its potential to address a multitude of diseases

Event and webcast today at 8 a.m. ET

CAMBRIDGE, UK, and BOSTON – December 14, 2023 – Bicycle Therapeutics (Nasdaq: BCYC), a biotechnology company pioneering a new and differentiated class of therapeutics based on its proprietary bicyclic peptide (Bicycle®) technology, is today hosting a Research & Development (R&D) Day for investors and analysts in New York to provide clinical updates for BT8009, BT7480 and BT5528, and an overview of the company's strategy and pipeline opportunities. The company will also highlight the broad capabilities of its novel Bicycle® platform technology. The event begins at 8 a.m. ET and will be available via webcast here.

"During our first R&D Day, we are excited to showcase the advantages of our Nobel Prize-winning science and our strategy to discover and develop therapies with greater tolerability that could provide enhanced benefit to a multitude of patients, starting with those who have cancer," said Kevin Lee, Ph.D., CEO of Bicycle Therapeutics. "Through our Nectin-4 and EphA2 portfolios and the continued work on our platform, including through partnerships, we are building a leading precision-guided therapeutics company with the potential to address a wide range of diseases that affect millions of people around the world. We believe that our technology has the potential to not only help patients live longer but also to live well."

"Today we are excited to provide clinical updates for our three lead programs," said Santiago Arroyo, M.D., Ph.D., Chief Development Officer of Bicycle Therapeutics. "In totality, the data support the emerging differentiated profile of our Bicycle® molecules, paving the way to deliver best-in-class or first-in-class therapies for many cancers. Based on our clinical updates, we are taking important next steps with our development programs, setting up what we expect to be a catalyst-rich 2024."

Key R&D Day Highlights

Nectin-4 Portfolio

Bicycle Therapeutics is advancing two clinical programs, BT8009 and BT7480, targeting Nectin-4, a well-validated tumor antigen with elevated levels of expression in multiple tumor types.

BT8009 is a Nectin-4 Bicycle toxin conjugate (BTC®) designed to overcome the significant toxicity associated with other toxin conjugate approaches. In the ongoing Phase 1/2 Duravelo-1 study involving heavily pre-treated patients, BT8009 showed:

- A promising response profile with a 38% objective response rate (ORR) in 26 patients with metastatic urothelial cancer (mUC) receiving 5 mg/m^2 weekly and who had not been treated with enfortumab vedotin (EV-naïve), and a median duration of response (mDOR) of 11.1 months in 10 patients with 5 responders still on therapy. This includes 1 complete response, 7 partial responses and 2 unconfirmed responses.
- Encouraging initial data in other cancers such as ovarian, triple-negative breast (TNBC) and non-small cell lung (NSCLC) that support further expansion beyond mUC.
- An emerging differentiated safety profile seen in 113 patients with various types of cancer receiving 5 mg/m^2 weekly, with treatment-related adverse events being primarily low in frequency and severity.
    - Adverse events of interest such as ocular disorders, peripheral neuropathy and skin reactions were low in frequency and severity. Importantly, treatment-related peripheral neuropathy was low-grade and often reversible, including zero cases of severe (≥Grade 3) peripheral sensory neuropathy (damage to the nerves that carry sensations like pain to the brain).
    - In 34 EV-naïve mUC patients, treatment-related adverse events and adverse events of interest were also low, similar to the 5 mg/m^2 weekly total safety study population. Notably, there were zero cases of severe (≥Grade 3) ocular disorders, peripheral neuropathy or skin reactions.
    - In 7 heavily pre-treated mUC patients receiving BT8009 5 mg/m^2 weekly in combination with pembrolizumab, an acceptable tolerability profile was observed with limited severe treatment-related adverse events, including zero cases of severe (≥Grade 3) ocular disorders, peripheral neuropathy or skin reactions.

Bicycle Therapeutics plans to initiate the Phase 2/3 Duravelo-2 registrational trial of BT8009 in patients with mUC in 1Q 2024 and intends to complete the Phase 1/2 Duravelo-1 open-label study across multiple cancers.

BT7480 is a Nectin-4 targeted CD137 agonist designed to overcome immune agonist toxicities and activate the immune system in Nectin-4 expressing tumors. Clinical development has been guided by safety considerations observed with first-generation CD137 agonists, the novelty of the Bicycle® platform technology and the U.S. Food and Drug Administration's (FDA) Project Optimus initiative. In a Phase 1 clinical trial, BT7480 showed:

- In 33 patients assigned to receive one of 9 different doses of BT7480, an emerging differentiated safety and tolerability profile with a low number of severe adverse events. The majority of the patients studied had tumors that expressed Nectin-4 and CD137.
- Two unconfirmed partial responses in heavily pre-treated patients with cervical cancer.
- Three prolonged stable disease (≥7 months) in NSCLC and anal cancer.

Bicycle Therapeutics will continue to define the recommended Phase 2 dose (or maximum dose) and dose range for BT7480, with a view to enroll combination cohorts with checkpoint inhibitors in 2024. These data will inform the design of a Phase 2 trial that could support potential accelerated approval of BT7480.

Ephrin-A2 (EphA2) Portfolio

Bicycle Therapeutics is advancing one clinical program, BT5528, and one preclinical program, BT7455, targeting EphA2, a tumor antigen that is widely expressed in many cancers and has historically been difficult to target. BT7455 is an EphA2-targeted CD137 agonist whose Investigational New Drug-enabling work is ongoing.

BT5528 is an EphA2 BTC® designed to overcome the significant toxicity associated with other toxin conjugate approaches that have been unsuccessful. In an ongoing Phase 1/2 clinical trial enrolling patients with various solid tumors, BT5528 showed:

- In 109 patients, an acceptable emerging tolerability profile with few severe adverse events. This was also seen in 74 patients receiving 6.5 mg/m^2 every other week, the dose being studied in various tumors in the expansion cohorts. Importantly, unlike other EphA2-targeted agents, no bleeding events were observed in patients treated with BT5528 at any dose.
- Encouraging early activity in mUC with a 39% ORR in 18 patients receiving 6.5 mg/m^2, 8.5 mg/m^2 or 10 mg/m^2 every other week, and an mDOR of 4 months in 7 patients with one responder still on therapy. This includes 6 partial responses and 1 unconfirmed response.
- Encouraging emerging data in other cancers such as ovarian, gastric/upper gastrointestinal and head and neck that are informing the dose optimization strategy and further development.

Given the promising tolerability profile of BT5528 at 6.5 mg/m^2 every other week and in line with the FDA's Project Optimus initiative, Bicycle Therapeutics has now commenced further cohorts in mUC and ovarian cancer to test 5 mg/m^2 weekly, which will inform decisions about dose optimization, potential drug combinations and expansion into other tumor types. Data from these cohorts are expected to be available in the second half of 2024.

Platform Opportunities

The company will highlight its progress in developing its next generation of Bicycle® conjugates, including:

- **Next generation BTCs:** Focusing on designing linkers specifically for BTCs, which may provide enhanced payload release into the tumor. The company plans to select a BTC® clinical candidate using next-generation technology in the second half of 2024.
- **Bicycle Radio Conjugates (BRC™):** Developing a pipeline of novel binders with optimized properties for radioisotope delivery. For example, preclinical studies of a BRC targeting MT1-MMP, a high-value target in cancer treatment, showed potent anti-tumor activity and a favorable tolerability profile. Over 2024, Bicycle Therapeutics intends to generate early human imaging data from its wholly owned BRC pipeline.
- **Beyond Oncology:** Successfully exploring other therapeutic applications of the Bicycle® platform technology using non-dilutive funding, demonstrating the platform's plug-and-play approach to precision targeting. For example, through partnerships with Dementia Discovery Fund and Ionis Therapeutics, the company demonstrated that delivery of therapies to the central nervous system, including across the blood brain barrier, can be achieved with Bicycle® molecules. Bicycle Therapeutics will continue to develop Bicycle® molecules to address disease outside of oncology through innovative partnerships.

About Bicycle Therapeutics

Bicycle Therapeutics is a clinical-stage biopharmaceutical company developing a novel class of medicines for diseases that are underserved by existing therapeutics. Bicycle® molecules are fully synthetic short peptides constrained with small molecule scaffolds to form two loops that stabilize their structural geometry. This constraint facilitates target binding with high affinity and selectivity, making Bicycle® molecules attractive candidates for drug development. The company is evaluating BT8009, a Bicycle Toxin Conjugate (BTC®) targeting Nectin-4, a well-validated tumor antigen; BT7480, a Bicycle TICA® targeting Nectin-4 and agonizing CD137; and BT5528, a BTC® targeting EphA2 in company-sponsored Phase 1/2 trials. In addition, BT1718, a BTC® that targets MT1-MMP, is being investigated in a Phase 1/2a clinical trial sponsored by the Cancer Research UK Centre for Drug Development. Bicycle Therapeutics is headquartered in Cambridge, UK, with many key functions and members of its leadership team located in Cambridge, Mass. For more information, visit bicycletherapeutics.com.

Forward Looking Statements

This press release may contain forward-looking statements made pursuant to the safe harbor provisions of the Private Securities Litigation Reform Act of 1995. These statements may be identified by words such as “aims,” “anticipates,” “believes,” “could,” “estimates,” “expects,” “forecasts,” “goal,” “intends,” “may,” “plans,” “possible,” “potential,” “seeks,” “will” and variations of these words or similar expressions that are intended to identify forward-looking statements, although not all forward-looking statements contain these words. Forward-looking statements in this press release include, but are not limited to, statements regarding Bicycle’s anticipated advancement of its current and prospective product candidates, including the timing of initiation and design of the Duravelo-2 Phase 2/3 clinical trial and potential accelerated approval of BT8009; the timing of initiation and design of a potential Phase 2 trial that could support accelerated approval for BT7480; the timing and conduct of combination cohorts for BT7480 with checkpoint inhibitors; the timing of initiation and design of clinical trials for BT5528; the timing of initiation of IND-enabling work for BT7455; the anticipated progression of Bicycle’s clinical trials and preclinical studies; the availability of and timing of updates for clinical candidates BT8009, BT5528 and BT7480; the therapeutic potential for Bicycle® molecules in bladder cancer and other oncologic indications, as well as other indications beyond oncology; and current and prospective collaborations. Bicycle may not actually achieve the plans, intentions or expectations disclosed in these forward-looking statements, and you should not place undue reliance on these forward-looking statements. Actual results or events could differ materially from the plans, intentions and expectations disclosed in these forward-looking statements as a result of various factors, including: uncertainties inherent in the initiation, progress and completion of clinical trials and preclinical studies and clinical and preclinical development of Bicycle’s product candidates; availability and timing of results from clinical trials; whether the outcomes of preclinical studies will be predictive of clinical trial results; whether initial or interim results from a clinical trial will be predictive of the final results of the trial or the results of future trials; the risk that trials may have unsatisfactory outcomes; potential adverse effects arising from the testing or use of Bicycle’s current or prospective product candidates; the risk that Bicycle may not maintain its current collaborations or enter into new collaborations in the future; and other important factors, any of which could cause Bicycle’s actual results to differ from those contained in the forward-looking statements, are described in greater detail in the section entitled “Risk Factors” in Bicycle’s Quarterly Report on Form 10-Q filed with the Securities and Exchange Commission (SEC) on November 2, 2023, as well as in other filings Bicycle may make with the SEC in the future. Any forward-looking statements contained in this press release speak only as of the date hereof, and Bicycle expressly disclaims any obligation to update any forward-looking statements contained herein, whether because of any new information, future events, changed circumstances or otherwise, except as otherwise required by law.

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